Clinical trial results:
201496: A Study to Evaluate the Efficacy and Safety of 15mg BID Losmapimod (GW856553) Compared to Placebo in Frequently Exacerbating Subjects with Chronic Obstructive Pulmonary Disease (COPD).

Summary

EudraCT number	2014-002992-27
Trial protocol	SK DE BG ES
Global end of trial date	30 June 2016

Results information

Result version number	v3 (current)
This version publication date	12 July 2018
First version publication date	08 March 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	201496

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the yearly rate of moderate-severe COPD exacerbations in losmapimod compared to placebo treated subjects.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 59
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	Spain: 8
Worldwide total number of subjects	190
EEA total number of subjects	103

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	90
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind (sponsor unblinded), parallel-group, multi-center study evaluating 15 milligrams (mg) twice daily (BID) of losmapimod versus placebo in addition to standard of care in male and female participants (par.) >=40 years of age having chronic obstructive pulmonary disease (COPD).

Pre-assignment

Screening details:

This study consisted of a 28 day screening period followed by treatment period (TP) of minimum 26 weeks. Total duration of TP was variable from 26 weeks to 52 weeks, and safety follow-up after 1 week. Total 365 par. were screened (175 par. failed), of which 190 par. passed screening and 184 par. were randomized in a TP.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablet was administered orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period.

Arm title	Losmapimod 15 mg

Arm description:

Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication.

Arm type	Experimental
Investigational medicinal product name	Losmapimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Losmapimod 15 mg tablet was administered orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period.

Number of subjects in period 1[1]	Placebo	Losmapimod 15 mg
Started	94	90
Completed	14	10
Not completed	80	80
Consent withdrawn by subject	1	4
Physician decision	1	1
Other: Study closed/terminated	66	55
Adverse Event, non-fatal	8	9
Other: Met stopping criteria	1	-
Lost to follow-up	-	2
Adverse Event, serious fatal	1	3
Lack of efficacy	1	3
Protocol deviation	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 190 enrolled participants, 184 were randomized in a TP.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication.	
Reporting group title	Losmapimod 15 mg
Reporting group description:	
Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication.	

Reporting group values	Placebo	Losmapimod 15 mg	Total
Number of subjects	94	90	184
Age categorical			
Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	64.6	66.4	
standard deviation	± 8.27	± 6.66	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	33	26	59
Male	61	64	125
Race/Ethnicity, Customized			
Race/ Ethnicity details were collected.			
Units: Subjects			
Japanese/East Asian /South East Asian Heritage	10	9	19
White	84	81	165

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication.

Reporting group title	Losmapimod 15 mg

Reporting group description:

Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication.

Primary: Annual rate of moderate and severe exacerbations of COPD

End point title	Annual rate of moderate and severe exacerbations of COPD

End point description:

An exacerbation of COPD, is defined as the worsening of 2 or more major symptoms (dyspnea, sputum volume, sputum purulence) or the worsening of any 1 major symptom together with any 1 of the minor symptoms (sore throat, cold, fever without other cause, increased cough and wheeze), for at least 2 consecutive days. Moderate-severe exacerbations were defined as use of antibiotics and/or oral steroids and/or hospitalization. Summary only included exacerbations for which a date of resolution or death was provided. Analysis was performed by using Bayesian inference assuming non-informative priors. The mean exacerbation rate was adjusted for treatment group, smoking status, ICS use and region. The adjusted posterior median was summarized per treatment group. The number of exacerbation events per participant was assumed to follow a negative binomial distribution. Modified Intent-to-Treat (mITT) Population comprised of all randomized par. who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

From the start of the study treatment up to 53 Weeks

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[1]	90[2]		
Units: Exacerbations per participant per year				
median (standard deviation)	0.84 (± 0.19)	0.88 (± 0.22)		

Notes:

[1] - mITT Population

[2] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Data presented above are for 95% equal-tailed credible intervals. The estimated posterior probability that the true ratio losmapimod/placebo is <1 assuming noninformative priors is 0.44.

Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted median
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.73
Variability estimate	Standard deviation
Dispersion value	0.28

Secondary: Time to first occurrence of moderate or severe COPD exacerbation

End point title	Time to first occurrence of moderate or severe COPD exacerbation

End point description:

The time to first moderate-severe COPD exacerbation in par. treated with losmapimod compared to placebo treated par. was evaluated. The time to the first on-treatment moderate-severe exacerbation was calculated as exacerbation onset date of first on-treatment exacerbation minus exposure start date plus 1. No statistical analysis was conducted. Data was summarized statistically only.

End point type	Secondary

End point timeframe:

From the start of the study treatment up to 53 Weeks

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[3]	90[4]		
Units: Days				
arithmetic mean (standard deviation)	168.01 (± 106.222)	160.18 (± 117.142)		

Notes:

[3] - mITT Population

[4] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants having any adverse events (AEs), Serious adverse events (SAEs)

End point title	Number of participants having any adverse events (AEs), Serious adverse events (SAEs)

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, any other

situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinaemia were categorized as SAE. AEs were considered as on-treatment If AE onset date is on or after treatment start date & on or before treatment stop date. par. having any AE or SAE were included in analysis.

End point type	Secondary

End point timeframe:

From the start of the study treatment up to 53 Weeks

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[5]	90[6]		
Units: Participants				
Non-serious AEs	34	38		
SAEs	8	19		

Notes:

[5] - mITT Population

[6] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in spirometry parameters in pre and post forced expiratory volume in 1 second (FEV1); pre and post forced vital capacity (FVC); pre and post forced expiratory volume in 6 seconds (FEV6).

End point title	Change from Baseline in spirometry parameters in pre and post forced expiratory volume in 1 second (FEV1); pre and post forced vital capacity (FVC); pre and post forced expiratory volume in 6 seconds (FEV6).

End point description:

Pre and post FEV1, FVC and FEV6 were performed at Screening, Day 1 pre-dose and Weeks 2, 4, 8, 12, 18, 26, 39 and 52. Par. were asked to withheld all bronchodilator therapy included ipratropiumn bromide and salbutamol/albuterol for at least 4 hours prior to prebronchodilator spirometric test. Post-bronchodilator spirometric assessment was performed after inhalation of 400/360 micograms (µg) of salbutamol/albuterol in 10-15 minutes. Day 1 (pre-dose) values were considered as Baseline values. Change from Baseline was calculated as value at the indicated time point minus Baseline value. The maximum value of the 3 replicate assessments were used. Analysis performed using a mixed-effects repeated measures model. The adjusted mean values were summarized per treatment group. Par. were included in the analysis if they had at least one post-baseline measurement. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 52

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[7]	90[8]		
Units: Liters				
arithmetic mean (standard error)				
FEV1 pre-dose, Week 2, n = 90, 83	0.002 (± 0.0241)	0.028 (± 0.0258)		
FEV1 Pre-dose, Week 4, n=88, 82	-0.010 (± 0.0242)	0.025 (± 0.0259)		
FEV1 Pre-dose, Week 8, n=81, 79	-0.031 (± 0.0247)	0.028 (± 0.0261)		
FEV1 Pre-dose, Week 12, n=78, 71	-0.011 (± 0.0250)	-0.014 (± 0.0267)		
FEV1 Pre-dose, Week 18, n=67, 61	-0.037 (± 0.0260)	0.013 (± 0.0277)		
FEV1 Pre-dose, Week 26, n=53, 52	-0.059 (± 0.0278)	0.020 (± 0.0289)		
FEV1 Pre-dose, Week 39, n=28, 28	-0.085 (± 0.0342)	0.001 (± 0.0353)		
FEV1 Pre-dose, Week 52, n=14, 11	-0.034 (± 0.0485)	0.016 (± 0.0513)		
FEV1 post-dose, Week 2, n=89, 82	0.012 (± 0.0188)	0.026 (± 0.0203)		
FEV1 post-dose, Week 4, n=87, 81	-0.022 (± 0.0193)	0.019 (± 0.0207)		
FEV1 post-dose, Week 8, n=80, 78	-0.010 (± 0.0232)	0.023 (± 0.0242)		
FEV1 post-dose, Week 12, n=76, 69	-0.008 (± 0.0217)	-0.020 (± 0.0231)		
FEV1 post-dose, Week 18, n=66, 60	-0.035 (± 0.0256)	-0.012 (± 0.0271)		
FEV1 post-dose, Week 26, n=52, 51	-0.070 (± 0.0273)	0.030 (± 0.0282)		
FEV1 post-dose, Week 39, n=27, 27	-0.086 (± 0.0346)	-0.031 (± 0.0356)		
FEV1 post-dose, Week 52, n=13, 10	-0.018 (± 0.0419)	0.024 (± 0.0472)		
FEV6 pre-dose, Week 2, n = 90,82	-0.007 (± 0.0353)	0.045 (± 0.0381)		
FEV6 Pre-dose, Week 4, n=87, 81	-0.034 (± 0.0353)	0.012 (± 0.0380)		
FEV6 Pre-dose, Week 8, n=81, 78	-0.043 (± 0.0400)	0.032 (± 0.0424)		
FEV6 Pre-dose, Week 12, n=78, 71	-0.036 (± 0.0366)	-0.034 (± 0.0392)		
FEV6 Pre-dose, Week 18, n=67, 60	-0.073 (± 0.0413)	-0.014 (± 0.0441)		
FEV6 Pre-dose, Week 26, n=53, 52	-0.076 (± 0.0405)	-0.003 (± 0.0425)		
FEV6 Pre-dose, Week 39, n=28, 28	-0.102 (± 0.0486)	0.013 (± 0.0507)		
FEV6 Pre-dose, Week 52, n=14, 11	-0.101 (± 0.0731)	0.071 (± 0.0745)		
FEV6 post-dose, Week 2, n=89, 81	-0.003 (± 0.0296)	0.023 (± 0.0319)		
FEV6 post-dose, Week 4, n=86, 80	-0.027 (± 0.0273)	0.010 (± 0.0295)		
FEV6 post-dose, Week 8, n=80, 76	-0.039 (± 0.0313)	0.012 (± 0.0331)		

FEV6 post-dose, Week 12, n=76, 69	-0.028 (± 0.0308)	-0.029 (± 0.0330)		
FEV6 post-dose, Week 18, n=66, 59	-0.060 (± 0.0367)	-0.035 (± 0.0392)		
FEV6 post-dose, Week 26, n=51, 51	-0.081 (± 0.0360)	0.003 (± 0.0373)		
FEV6 post-dose, Week 39, n=27, 27	-0.095 (± 0.0428)	-0.067 (± 0.0443)		
FEV6 post-dose, Week 52, n=13, 10	-0.119 (± 0.0607)	-0.017 (± 0.0674)		
FVC, Pre-dose, Week 2, n =90, 83	-0.018 (± 0.0389)	0.038 (± 0.0417)		
FVC, Pre-dose, Week 4, n =88, 82	-0.039 (± 0.0392)	0.006 (± 0.0418)		
FVC, Pre-dose Week 8, n = 81, 79	-0.061 (± 0.0401)	0.011 (± 0.0422)		
FVC, Pre-dose, Week 12, n =78, 71	-0.046 (± 0.0405)	-0.058 (± 0.0430)		
FVC, Pre-dose Week 18, n =67, 61	-0.093 (± 0.0422)	-0.021 (± 0.0447)		
FVC, Week 26, n=53, 52	-0.095 (± 0.0451)	-0.028 (± 0.0468)		
FVC, Pre-dose Week 39, n =28, 28	-0.115 (± 0.0558)	-0.033 (± 0.0574)		
FVC, Pre-dose Week 52, n =14, 11	-0.052 (± 0.0806)	0.031 (± 0.0837)		
FVC, Post-dose Week 2, n =89, 82	-0.007 (± 0.0359)	0.037 (± 0.0385)		
FVC, Post-dose Week 4, n =87, 81	-0.021 (± 0.0316)	0.033 (± 0.0341)		
FVC, Post-dose Week 8, n =80, 78	-0.052 (± 0.0366)	0.019 (± 0.0385)		
FVC,Post-dose Week 12, n =76, 69	-0.020 (± 0.0361)	-0.008 (± 0.0385)		
FVC, Post-dose Week 18, n =66, 60	-0.075 (± 0.0422)	-0.016 (± 0.0449)		
FVC, Post-dose Week 26, n=52, 51	-0.135 (± 0.0495)	0.003 (± 0.0513)		
FVC, Post-dose Week 39, n =27, 27	-0.092 (± 0.0499)	-0.043 (± 0.0518)		
FVC, Post-dose Week 52, n =13, 10	-0.081 (± 0.0612)	-0.039 (± 0.0671)		

Notes:

[7] - mITT Population

[8] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: FEV1 pre-dose, Week 2	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.371 [9]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.026

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.084

Notes:

[9] - Analysis performed using a Mixed-effect Model Repeated Measures (MMRM) with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
FEV1 pre-dose, Week 4	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.244 [10]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.093

Notes:

[10] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
FEV1 pre-dose, Week 8	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05 [11]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.119

Notes:

[11] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:	
FEV1 pre-dose, Week 12	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.942 [12]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.058

Notes:

[12] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
FEV1 pre-dose, Week 18	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127 [13]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.114

Notes:

[13] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
FEV1 pre-dose, Week 26	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.024 [14]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.079

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.148

Notes:

[14] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 7
Statistical analysis description:	
FEV1 pre-dose, Week 39	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.057 [15]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.174

Notes:

[15] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
FEV1 pre-dose, Week 52	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.481 [16]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.191

Notes:

[16] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 9

Statistical analysis description:	
FEV1 post-dose, Week 2	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521 [17]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.059

Notes:

[17] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 10
Statistical analysis description:	
FEV1 post-dose, Week 4	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.084 [18]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.086

Notes:

[18] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 11
Statistical analysis description:	
FEV1 post-dose, Week 8	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266 [19]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.033

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.09

Notes:

[19] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 12
Statistical analysis description:	
FEV1 post-dose, Week 12	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.665 [20]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.042

Notes:

[20] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 13
Statistical analysis description:	
FEV1 post-dose, Week 18	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.489 [21]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043
upper limit	0.09

Notes:

[21] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 14

Statistical analysis description:	
FEV1 post-dose, Week 26	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [22]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.17

Notes:

[22] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 15
Statistical analysis description:	
FEV1 post-dose, Week 39	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.248 [23]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.148

Notes:

[23] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 16
Statistical analysis description:	
FEV1 post-dose, Week 52	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.506 [24]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.043

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.087
upper limit	0.172

Notes:

[24] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 17
Statistical analysis description:	
FEV6 pre-dose, Week 2	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.223 [25]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.134

Notes:

[25] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 18
Statistical analysis description:	
FEV6 pre-dose, Week 4	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [26]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.129

Notes:

[26] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 19

Statistical analysis description:	
FEV6 pre-dose, Week 8	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131 [27]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.173

Notes:

[27] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 20
Statistical analysis description:	
FEV6 pre-dose, Week 12	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949 [28]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	0.09

Notes:

[28] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 21
Statistical analysis description:	
FEV6 pre-dose, Week 18	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259 [29]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.059

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.044
upper limit	0.163

Notes:

[29] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 22
Statistical analysis description:	
FEV6 pre-dose, Week 26	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152 [30]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.172

Notes:

[30] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 23
Statistical analysis description:	
FEV6 pre-dose, Week 39	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076 [31]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.241

Notes:

[31] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 24

Statistical analysis description:	
FEV6 pre-dose, Week 52	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107 [32]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.381

Notes:

[32] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 25
Statistical analysis description:	
FEV6 post-dose, Week 2	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484 [33]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.097

Notes:

[33] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 26
Statistical analysis description:	
FEV6 post-dose, Week 4	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.256 [34]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.037

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.1

Notes:

[34] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 27
Statistical analysis description:	
FEV6 post-dose, Week 8	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.184 [35]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.128

Notes:

[35] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 28
Statistical analysis description:	
FEV6 post-dose, Week 12	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [36]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.077
upper limit	0.074

Notes:

[36] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 29

Statistical analysis description:	
FEV6 post-dose, Week 18	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.608 [37]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.12

Notes:

[37] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 30
Statistical analysis description:	
FEV6 post-dose, Week 26	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071 [38]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.175

Notes:

[38] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 31
Statistical analysis description:	
FEV6 post-dose, Week 39	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.622 [39]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.028

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.141

Notes:

[39] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 32
Statistical analysis description:	
FEV6 post-dose, Week 52	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.277 [40]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.102
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.086
upper limit	0.291

Notes:

[40] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 33
Statistical analysis description:	
FVC Pre-dose, Week 2	
Comparison groups	Losmapimod 15 mg v Placebo
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241 [41]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.15

Notes:

[41] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 34

Statistical analysis description:	
FVC Pre-dose, Week 4	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.348 [42]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.14

Notes:

[42] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 35
Statistical analysis description:	
FVC Pre-dose, Week 8	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138 [43]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.169

Notes:

[43] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 36
Statistical analysis description:	
FVC Pre-dose, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.813 [44]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	0.087

Notes:

[44] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 37
Statistical analysis description:	
FVC Pre-dose, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172 [45]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.177

Notes:

[45] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 38
Statistical analysis description:	
FVC Pre-dose, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242 [46]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.18

Notes:

[46] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 39

Statistical analysis description:	
FVC Pre-dose, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.267 [47]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.228

Notes:

[47] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 40
Statistical analysis description:	
FVC Pre-dose, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.471 [48]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.143
upper limit	0.309

Notes:

[48] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 41
Statistical analysis description:	
FVC Post-dose, Week 2	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.315 [49]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.045

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043
upper limit	0.132

Notes:

[49] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 42
Statistical analysis description:	
FVC Post-dose, Week 4	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.143 [50]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.126

Notes:

[50] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 43
Statistical analysis description:	
FVC Post-dose, Week 8	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111 [51]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.16

Notes:

[51] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 44

Statistical analysis description:	
FVC Post-dose, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783 [52]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	0.1

Notes:

[52] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 45
Statistical analysis description:	
FVC Post-dose, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283 [53]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.167

Notes:

[53] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 46
Statistical analysis description:	
FVC Post-dose, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038 [54]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.138

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.267

Notes:

[54] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 47
Statistical analysis description:	
FVC Post-dose, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.467 [55]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.18

Notes:

[55] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 48
Statistical analysis description:	
FVC Post-dose, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64 [56]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.138
upper limit	0.222

Notes:

[56] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Secondary: Change from Baseline in spirometry parameters in pre and post FEV1/FVC, Percent Predicted (PP) FEV1, PP FEV6 and PP FVC

End point title	Change from Baseline in spirometry parameters in pre and post FEV1/FVC, Percent Predicted (PP) FEV1, PP FEV6 and PP FVC

End point description:

Pre and post FEV1/FVC, PP FEV1, PP FEV6 and PP FVC were assessed at Screening, Day 1 pre-dose and Weeks 2, 4, 8, 12, 18, 26, 39 and 52. Par. were asked to withheld all bronchodilator therapy included ipratropiumn bromide and salbutamol/albuterol for at least 4 hours prior to the prebronchodilator spirometric test. Post-bronchodilator spirometric assessment was performed after inhalation of 400/360 µg of salbutamol/albuterol in 10-15 minutes. Day 1 (pre-dose) values were considered as Baseline values. Change from Baseline was calculated as value at indicated time point minus Baseline value. The maximum value of the 3 replicate assessments were used. Analysis performed using a mixed-effects repeated measures model. The adjusted mean values were summarized per treatment group. Par. were included in the analysis if they had at least one post-baseline measurement. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 52

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[57]	90[58]		
Units: Percentage				
arithmetic mean (standard error)				
PP FVC, Week 2, n =90, 82	0.72 (± 1.156)	1.31 (± 1.228)		
PP FVC, Week 4, n =88, 81	-0.73 (± 1.160)	1.72 (± 1.228)		
PP FVC, Week 8, n =81, 78	-2.05 (± 1.556)	0.47 (± 1.604)		
PP FVC, Week 12 , n =78, 70	-0.64 (± 1.324)	-0.78 (± 1.399)		
PP FVC, Week 18, n =67, 60	-1.58 (± 1.286)	1.12 (± 1.356)		
PP FVC, Week 26, n =53, 51	-2.81 (± 1.518)	1.88 (± 1.575)		
PP FVC, Week 39, n =28, 27	-2.06 (± 1.548)	1.24 (± 1.604)		
PP FVC, Week 52, n =14, 11	-1.24 (± 2.017)	0.92 (± 2.137)		
PP FEV1, Week 2, n =90, 82	0.28 (± 0.858)	2.03 (± 0.932)		
PP FEV1, Week 4, n =88, 81	-0.24 (± 0.877)	1.52 (± 0.950)		
PP FEV1, Week 8, n =81, 78	-1.14 (± 0.979)	1.04 (± 1.037)		
PP FEV1, Week 12 , n =78, 70	-0.10 (± 0.940)	0.12 (± 1.013)		
PP FEV1, Week 18, n =67, 60	-0.79 (± 1.094)	0.58 (± 1.172)		
PP FEV1, Week 26, n =53, 51	-2.07 (± 1.075)	1.26 (± 1.134)		
PP FEV1, Week 39, n =28, 27	-2.33 (± 1.307)	0.79 (± 1.370)		
PP FEV1, Week 52, n =14, 11	-0.32 (± 1.714)	2.03 (± 1.901)		
PP FEV6, Week 2, n =87, 75	0.63 (± 1.163)	3.45 (± 1.252)		
PP FEV6, Week 4, n =84, 75	-0.72 (± 1.135)	2.15 (± 1.212)		

PP FEV6, Week 8, n =79, 74	-1.71 (± 1.332)	2.04 (± 1.395)		
PP FEV6, Week 12 , n =76, 67	-0.42 (± 1.214)	-0.02 (± 1.284)		
PP FEV6, Week 18, n =65, 56	-1.47 (± 1.347)	1.87 (± 1.438)		
PP FEV6, Week 26, n =51, 48	-1.69 (± 1.359)	1.84 (± 1.436)		
PP FEV6, Week 39, n =26, 24	-2.10 (± 1.543)	2.09 (± 1.652)		
PP FEV6, Week 52, n =13, 11	0.99 (± 2.936)	3.66 (± 3.209)		
FEV1/FVC, Pre-dose, Week 2, n =90, 83	0.22 (± 0.571)	0.43 (± 0.611)		
FEV1/FVC, Pre-dose, Week 4, n =88, 82	0.30 (± 0.674)	0.43 (± 0.716)		
FEV1/FVC, Pre-dose Week 8, n = 81, 79	0.10 (± 0.632)	0.46 (± 0.663)		
FVC, Pre-dose, Week 12, n =78, 71	0.31 (± 0.649)	0.02 (± 0.688)		
FEV1/FVC, Pre-dose Week 18, n =67, 61	0.11 (± 0.735)	0.34 (± 0.780)		
FEV1/FVC, Week 26, n=53, 52	-0.48 (± 0.767)	0.84 (± 0.803)		
FEV1/FVC, Pre-dose Week 39, n =28, 28	-1.36 (± 0.932)	0.70 (± 0.963)		
FEV1/FVC, Pre-dose Week 52, n =14, 11	-0.18 (± 1.177)	1.26 (± 1.270)		
FEV1/FVC, Post-dose Week 2, n =89, 82	0.09 (± 0.682)	0.51 (± 0.726)		
FEV1/FVC, Post-dose Week 4, n =87, 81	-0.90 (± 0.619)	-0.23 (± 0.662)		
FEV1/FVC, Post-dose Week 8, n =80, 78	0.12 (± 0.646)	0.28 (± 0.679)		
FEV1/FVC,Post-dose Week 12, n =76, 69	-0.51 (± 0.693)	-0.97 (± 0.736)		
FEV1/FVC, Post-dose Week 18, n =66, 60	-0.65 (± 0.643)	-0.23 (± 0.682)		
FEV1/FEV1/FVC, Post-dose Week 26, n=52, 51	-0.60 (± 2.272)	3.23 (± 2.292)		
FEV1/FVC, Post-dose Week 39, n =27, 27	-1.27 (± 0.939)	0.18 (± 0.961)		
FEV1/FVC, Post-dose Week 52, n =13, 10	0.34 (± 1.280)	1.51 (± 1.397)		

Notes:

[57] - mITT Population

[58] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
PP FVC, Week 2	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.661 [59]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	3.27

Notes:

[59] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

PP FVC, Week 6

Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.074 [60]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	5.12

Notes:

[60] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

PP FVC, Week 8

Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.21 [61]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	6.46

Notes:

[61] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 4

Statistical analysis description:	
PP FVC, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.933 [62]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.12

Notes:

[62] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
PP FVC, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.091 [63]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	5.82

Notes:

[63] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
PP FVC, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.018 [64]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	4.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	8.56

Notes:

[64] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 7
Statistical analysis description:	
PP FVC, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.103 [65]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	7.29

Notes:

[65] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
PP FVC, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.448 [66]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	7.82

Notes:

[66] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 9

Statistical analysis description:	
PP FEV1, Week 2	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.089 [67]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	3.77

Notes:

[67] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 10
Statistical analysis description:	
PP FEV1, Week 4	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.095 [68]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	3.84

Notes:

[68] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 11
Statistical analysis description:	
PP FEV1, Week 8	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.073 [69]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.19

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	4.58

Notes:

[69] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 12
Statistical analysis description:	
PP FEV1, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.853 [70]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	2.51

Notes:

[70] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 13
Statistical analysis description:	
PP FEV1, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.334 [71]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	4.17

Notes:

[71] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 14

Statistical analysis description:	
PP FEV1, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.017 [72]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	6.05

Notes:

[72] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 15
Statistical analysis description:	
PP FEV1, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.077 [73]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	6.59

Notes:

[73] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 16
Statistical analysis description:	
PP FEV1, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.355 [74]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	7.38

Notes:

[74] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 17
Statistical analysis description:	
PP FEV6, Week 2	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.044 [75]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	5.55

Notes:

[75] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 18
Statistical analysis description:	
PP FEV6, Week 4	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.032 [76]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	5.49

Notes:

[76] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 19

Statistical analysis description:	
PP FEV6, Week 8	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.025 [77]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	7.01

Notes:

[77] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 20
Statistical analysis description:	
PP FEV6, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.785 [78]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	3.29

Notes:

[78] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 21
Statistical analysis description:	
PP FEV6, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.052 [79]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	6.7

Notes:

[79] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 22
Statistical analysis description:	
PP FEV6, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.041 [80]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	6.92

Notes:

[80] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 23
Statistical analysis description:	
PP FEV6, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.043 [81]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	4.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	8.25

Notes:

[81] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 24

Statistical analysis description:	
PP FEV6, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.562 [82]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.58
upper limit	11.92

Notes:

[82] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 25
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 2	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.746 [83]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	1.52

Notes:

[83] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 26
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 4	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.878 [84]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.53
upper limit	1.79

Notes:

[84] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 27
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 8	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.644 [85]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	1.85

Notes:

[85] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 28
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.715 [86]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.86
upper limit	1.28

Notes:

[86] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 29

Statistical analysis description:	
Pre-dose FEV1/FVC, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.803 [87]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	2.1

Notes:

[87] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 30
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.184 [88]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	3.27

Notes:

[88] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 31
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.102 [89]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	2.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	4.52

Notes:

[89] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 32
Statistical analysis description:	
Pre-dose FEV1/FVC, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.383 [90]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.85
upper limit	4.73

Notes:

[90] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 33
Statistical analysis description:	
Post-dose FEV1/FVC, Week 2	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.607 [91]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.06

Notes:

[91] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 34

Statistical analysis description:	
Post-dose FEV1/FVC, Week 4	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.348 [92]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	2.08

Notes:

[92] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 35
Statistical analysis description:	
Post-dose FEV1/FVC, Week 8	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.826 [93]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	1.65

Notes:

[93] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 36
Statistical analysis description:	
Post-dose FEV1/FVC, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.588 [94]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	1.21

Notes:

[94] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 37
Statistical analysis description:	
Post-dose FEV1/FVC, Week 18	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.585 [95]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	1.91

Notes:

[95] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 38
Statistical analysis description:	
Post-dose FEV1/FVC, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.231 [96]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	3.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	10.12

Notes:

[96] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 39

Statistical analysis description:	
Post-dose FEV1/FVC, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.24 [97]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	3.89

Notes:

[97] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Statistical analysis title	Statistical analysis 40
Statistical analysis description:	
Post-dose FEV1/FVC, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.517 [98]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.49
upper limit	4.84

Notes:

[98] - Analysis performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment and Baseline by visit interactions. Toeplitz structure was used.

Secondary: Number of participants with electrocardiogram (ECG) findings

End point title	Number of participants with electrocardiogram (ECG) findings

End point description:

12-lead ECGs were obtained in triplicate at Screening then singly at Baseline (day 1, pre-dose) and post dose at Weeks 2, 4, 8, 12, 26, 39, 52 and at follow up (Week 53) using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QT duration corrected for heart rate by Fridericia's formula (QTcF) or QT duration corrected for heart rate by Bazett's formula (QTcB) intervals. Change in ECG findings were categorized as normal and abnormal. Abnormal ECG values could be clinically significant (CS) or not clinically significant (NCS), as determined by the investigator. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Up to 53 Weeks

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[99]	90[100]		
Units: Participants				
Normal-SCREENING, (n=94,90)	49	51		
Abnormal-NCS-SCREENING, (n=94,90)	39	36		
Abnormal-CS-SCREENING, (n=94,90)	9	5		
Normal-Baseline, (n=94,90)	44	54		
Abnormal-NCS-Baseline, (n=94,90)	46	31		
Abnormal-CS-Baseline, (n=94,90)	4	5		
Normal-Week 2, (n=90,84)	40	52		
Abnormal-NCS-Week 2, (n=90,84)	45	29		
Abnormal-CS-Week 2, (n=90,84)	5	3		
Normal-Week 4, (n=89,82)	45	53		
Abnormal-NCS-Week 4, (n=89,82)	40	27		
Abnormal-CS-Week 4, (n=89,82)	4	2		
Normal-Week 8, (n=80,80)	42	50		
Abnormal-NCS-Week 8, (n=80,80)	35	28		
Abnormal-CS-Week 8, (n=80,80)	3	2		
Normal-Week 12, (n=78,72)	45	42		
Abnormal-NCS-Week 12, (n=78,72)	29	29		
Abnormal-CS-Week 12, (n=78,72)	4	1		
Normal-Week 26, (n=53,52)	31	35		
Abnormal-NCS-Week 26, (n=53,52)	21	16		
Abnormal-CS-Week 26, (n=53,52)	1	1		
Normal-Week 39, (n=28,29)	18	20		
Abnormal-NCS-Week 39, (n=28,29)	9	8		
Abnormal-CS-Week 39, (n=28,29)	1	1		
Normal-Week 52, (n=14,11)	11	7		
Abnormal-NCS-Week 52, (n=14,11)	2	4		
Abnormal-CS-Week 52, (n=14,11)	1	0		
Normal-Follow up, (n=83,68)	37	42		
Abnormal-NCS-Follow up, (n=83,68)	40	25		
Abnormal-CS-Follow up, (n=83,68)	6	1		

Notes:

[99] - mITT Population

[100] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the indicated time points

End point title	Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the indicated time points

End point description:

SBP and DBP were taken at Screening, Baseline (day 1, pre-dose) and post dose at Weeks 2, 4, 8, 12,

26, 39, 52 and at follow up (Week 53). Measurements were taken in a semi-recumbent position after 5 minutes rest. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The Baseline value of an assessment is defined as the value at day 1, pre-dose. Par. were included in the analysis if they had at least one post-baseline measurement. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[101]	90[102]		
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP, Week 2, (n=90,84)	0.2 (± 12.00)	-2.9 (± 11.85)		
SBP, Week 4, (n=89,82)	-0.8 (± 11.49)	-0.4 (± 12.49)		
SBP, Week 8, (n=81,80)	-1.9 (± 14.53)	-0.3 (± 11.48)		
SBP, Week 12, (n=78,72)	0.5 (± 12.97)	-1.6 (± 13.84)		
SBP, Week 26, (n=53,53)	-1.5 (± 15.39)	-1.3 (± 13.25)		
SBP, Week 39, (n=28,29)	0.3 (± 16.30)	-3.4 (± 10.99)		
SBP, Week 52, (n=14,11)	6.1 (± 17.81)	-7.6 (± 12.89)		
SBP, Follow up, (n=83,68)	1.8 (± 14.46)	0.2 (± 13.41)		
DBP, Week 2, (n=90,84)	0.0 (± 7.18)	-3.8 (± 9.81)		
DBP, Week 4, (n=89,82)	-0.3 (± 8.57)	-2.2 (± 9.32)		
DBP, Week 8, (n=81,80)	-1.4 (± 8.75)	-1.5 (± 7.92)		
DBP, Week 12, (n=78,72)	1.5 (± 9.79)	-1.5 (± 9.59)		
DBP, Week 26, (n=53,53)	0.9 (± 8.33)	-1.2 (± 7.87)		
DBP, Week 39, (n=28,29)	-0.5 (± 10.40)	-1.9 (± 9.58)		
DBP, Week 52, (n=14,11)	3.4 (± 8.08)	-0.2 (± 8.46)		
DBP, Follow up, (n=83,68)	1.5 (± 10.57)	-1.7 (± 9.94)		

Notes:

[101] - mITT Population

[102] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate (HR) values at the indicated time points

End point title	Change from Baseline in heart rate (HR) values at the indicated time points

End point description:

HR was assessed at Screening, Baseline (day 1, pre-dose) and post dose at Weeks 2, 4, 8, 12, 26, 39, 52 and at follow up (Week 53). Measurements were taken in a semi-recumbent position after 5 minutes rest. Change from Baseline was calculated as the post-Baseline value minus the Baseline value. The Baseline value of an assessment is defined as the value at day 1, pre-dose. Par. were included in the analysis if they had at least one post-baseline measurement. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[103]	90[104]		
Units: Beats per minute (bpm)				
arithmetic mean (standard deviation)				
HR, Week 2, (n=90,84)	1.2 (± 7.99)	1.5 (± 9.92)		
HR, Week 4, (n=89,82)	1.4 (± 7.18)	0.6 (± 8.72)		
HR, Week 8, (n=81,80)	1.0 (± 8.39)	1.6 (± 9.50)		
HR, Week 12, (n=78,72)	3.3 (± 8.80)	2.2 (± 8.89)		
HR, Week 26, (n=53,53)	4.1 (± 10.99)	1.8 (± 8.32)		
HR, Week 39, (n=28,29)	3.3 (± 9.48)	4.4 (± 12.64)		
HR, Week 52, (n=14,11)	4.3 (± 9.55)	1.3 (± 8.72)		
HR, Follow up, (n=83,68)	3.6 (± 6.72)	4.2 (± 10.99)		

Notes:

[103] - mITT Population

[104] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Losmapimod area under the plasma concentration time curve (AUC) from time zero to the end of dosing interval (AUC[0-tau])

End point title	Plasma Losmapimod area under the plasma concentration time curve (AUC) from time zero to the end of dosing interval (AUC[0-tau])[105]

End point description:

Pharmacokinetics (PK) of losmapimod was evaluated in participants with COPD using PK samples collected at pre-dose at Week 2 and Week 12. At Week 26, a sample was collected at pre-dose and a second sample was collected at 2 hours post-dose. Par. of mITT population that provided at least one observed concentration data in this study were considered for PK analysis. Drug plasma concentration-time data were modelled by nonlinear mixed effects modelling. AUC[0-tau] (tau=12 hours) was estimated from the model.

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 2 and 12; pre-dose and at 2 hours post-dose at Week 26

Notes:

[105] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Losmapimod 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	85[106]			
Units: hour (h)*nanogram (ng)/milliliter (mL)				
geometric mean (confidence interval 95%)	668.5 (361.7 to 1235.6)			

Notes:

[106] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma losmapimod maximum concentration (Cmax) and lowest concentration (Ctrough) at steady state

End point title	Plasma losmapimod maximum concentration (Cmax) and lowest concentration (Ctrough) at steady state[107]

End point description:

Pharmacokinetics of losmapimod was evaluated in participants with COPD using PK samples collected at pre-dose at Week 2 and Week 12. At Week 26, a sample was collected at pre-dose and a second sample was collected at 2 hours post-dose. Par. of mITT population that provided at least one observed concentration data in this study were considered for PK analysis (represented by n=X, X in the category titles). Drug plasma concentration-time data were modelled by nonlinear mixed effects modelling to develop a Population PK model. Cmax and Ctrough were estimated from the PK model.

End point type	Secondary

End point timeframe:

Pre-dose at Weeks 2 and 12; pre-dose and at 2 hours post-dose at Week 26

Notes:

[107] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Losmapimod 15 mg			
Subject group type	Reporting group			
Number of subjects analysed	85[108]			
Units: ng/ mL				
geometric mean (confidence interval 95%)				
Cmax	49.7 (17.6 to 140.5)			
Ctrough	23.7 (12.9 to 43.3)			

Notes:

[108] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in frequency of short acting beta-agonist or anti-cholinergic use

End point title	Change from Baseline in frequency of short acting beta-agonist or anti-cholinergic use

End point description:

Use of short acting bronchodilators (short-acting beta2-agonists or short-acting anti-cholinergic) was allowed and was recorded in daily patient diary. It included inhaled short-acting beta2-agonists (e.g. Ipratropium bromide, salbutamol, Ipratropium/salbutamol (albuterol) combination product) and short-acting anti-cholinergics (e.g., ipratropium bromide3). Use of these medications was allowed throughout the study except 4 hours prior to and during each clinic visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 52

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[109]	90[110]		
Units: Average number of puffs per 24 hours				
arithmetic mean (standard deviation)				
Week 4; n=85, 82	-0.0029 (± 0.73616)	-0.0400 (± 0.93329)		
Week 8; n=79, 79	0.1143 (± 0.77946)	-0.1473 (± 1.26462)		
Week 12; n=76, 70	0.0904 (± 1.06920)	0.0022 (± 1.10426)		
Week 18; n=65, 61	0.3163 (± 1.26883)	0.1489 (± 0.97966)		
Week 26; n=51, 53	0.2725 (± 1.43462)	0.2098 (± 1.25768)		
Week 39; n=27, 27	0.7109 (± 1.61447)	0.3418 (± 1.39346)		
Week 52; n=14, 10	0.4368 (± 1.22619)	-0.2881 (± 0.98057)		

Notes:

[109] - mITT Population

[110] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in St Georges Respiratory Questionnaire (SGRQ) total, SGRQ symptoms score, SGRQ activity score and SGRQ impact score over time

End point title	Change from Baseline in St Georges Respiratory Questionnaire (SGRQ) total, SGRQ symptoms score, SGRQ activity score and SGRQ impact score over time

End point description:

SGRQ-C is a health related quality of life questionnaire consisting of 14 questions. SGRQ-C total score was calculated as 100 multiplied by summed weights from all positive items divided by sum of weights for all items in questionnaire. Components (Activity, Symptoms, Impacts) were calculated as 100 multiplied by summed weights from all positive items in that component divided by sum of weights for all items in that component. Score range for SGRQ-C total is 0-100. Maximum weights for Activity, Symptoms and Impacts component is 982.9, 566.2 and 1652.8 respectively. SGRQ-C was transformed to SGRQ for reporting. Higher scores indicate greater disease impact. Score at Day 1, pre-dose (Week 0) was considered as Baseline. Change from Baseline was calculated as score at indicated time point minus Baseline value. Only those par. with analyzable data at the given time points (represented by

n=X, X in category titles) were included in analysis.

End point type	Secondary

End point timeframe:

Baseline and up to Week 52

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[111]	90[112]		
Units: Scores on a scale				
least squares mean (standard error)				
SGRQ Total, Week 12, (n=74, 71)	-0.75 (± 1.541)	-1.42 (± 1.638)		
SGRQ Total, Week 26, (n=50, 49)	-2.20 (± 1.833)	-1.31 (± 1.904)		
SGRQ Total, Week 39, (n=28, 28)	-0.37 (± 2.451)	-3.19 (± 2.502)		
SGRQ Total, Week 52, (n=14, 11)	-2.95 (± 2.769)	-3.43 (± 3.098)		
SGRQ Symptoms, Week 12, (n=78, 72)	-2.41 (± 1.999)	-4.08 (± 2.115)		
SGRQ Symptoms, Week 26, (n=52, 52)	-5.04 (± 2.264)	-4.30 (± 2.335)		
SGRQ Symptoms, Week 39, (n=28, 29)	-4.61 (± 3.411)	-8.21 (± 3.370)		
SGRQ Symptoms, Week 52, (n=14, 11)	-3.69 (± 3.990)	-11.67 (± 4.296)		
SGRQ Activity, Week 12, (n=77, 71)	-0.08 (± 1.968)	1.15 (± 2.097)		
SGRQ Activity, Week 26, (n=50, 49)	-0.33 (± 2.217)	0.70 (± 2.303)		
SGRQ Activity, Week 39, (n=28, 28)	1.41 (± 3.027)	-1.00 (± 3.095)		
SGRQ Activity, Week 52, (n=14, 11)	-1.80 (± 3.308)	2.59 (± 3.650)		
SGRQ Impact, Week 12, (n=75, 71)	-0.53 (± 1.780)	-2.22 (± 1.893)		
SGRQ Impact, Week 26, (n=52, 50)	-1.84 (± 2.169)	-2.19 (± 2.255)		
SGRQ Impact, Week 39, (n=28, 28)	-0.59 (± 2.868)	-2.80 (± 2.931)		
SGRQ Impact, Week 52, (n=14, 11)	-2.01 (± 3.693)	-3.31 (± 4.099)		

Notes:

[111] - mITT Population

[112] - mITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

SGRQ Total, Week 12

Comparison groups	Placebo v Losmapimod 15 mg

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.706 [113]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	2.85

Notes:

[113] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
SGRQ Total, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.694 [114]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.58
upper limit	5.36

Notes:

[114] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
SGRQ Total, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.382 [115]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.23
upper limit	3.58

Notes:

[115] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
SGRQ Total, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.903 [116]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.54
upper limit	7.57

Notes:

[116] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
SGRQ Symptoms, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.481 [117]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.33
upper limit	2.99

Notes:

[117] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 6

Statistical analysis description:	
SGRQ Symptoms, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.793 [118]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.79
upper limit	6.25

Notes:

[118] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 7
Statistical analysis description:	
SGRQ Symptoms, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.421 [119]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.45
upper limit	5.26

Notes:

[119] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 8
Statistical analysis description:	
SGRQ Symptoms, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.162 [120]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-7.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.35
upper limit	3.4

Notes:

[120] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 9
Statistical analysis description:	
SGRQ Activity, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.592 [121]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.31
upper limit	5.78

Notes:

[121] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 10
Statistical analysis description:	
SGRQ Activity, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.704 [122]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.31
upper limit	6.36

Notes:

[122] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 11

Statistical analysis description:	
SGRQ Activity, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.546 [123]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.32
upper limit	5.5

Notes:

[123] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 12
Statistical analysis description:	
SGRQ Activity, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.35 [124]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.06
upper limit	13.84

Notes:

[124] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 13
Statistical analysis description:	
SGRQ Impact, Week 12	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.411 [125]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.75
upper limit	2.37

Notes:

[125] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 14
Statistical analysis description:	
SGRQ Impact, Week 26	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.896 [126]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.67
upper limit	4.97

Notes:

[126] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 15
Statistical analysis description:	
SGRQ Impact, Week 39	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.559 [127]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.73
upper limit	5.3

Notes:

[127] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Statistical analysis title	Statistical analysis 16

Statistical analysis description:	
SGRQ Impact, Week 52	
Comparison groups	Placebo v Losmapimod 15 mg
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.809 [128]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.19
upper limit	9.6

Notes:

[128] - Analysis was performed using a mixed-effects repeated measures model with covariates of treatment, smoking status at Screening, ICS use, region, Baseline, visit, treatment by visit and Baseline by visit interactions.

Secondary: Number of participants with abnormal liver events during the treatment period

End point title	Number of participants with abnormal liver events during the treatment period

End point description:

Various liver chemistry parameters were monitored periodically to ensure the safety and tolerability of Losmapimod as compared to placebo. Study treatments were discontinued for par. if alanine aminotransferase (ALT) absolute >= 5xupper limit of normal (ULN) or; ALT >= 3xULN persists for >=4 Weeks or; ALT>=3x ULN and bilirubin >=2xULN or; ALT>=3x ULN and International normalized ratio (INR) >=1.5 or; ALT>=3x ULN and cannot be monitored weekly for 4 Weeks or; ALT>=3x ULN symptomatic.

End point type	Secondary

End point timeframe:

Up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[129]	90[130]		
Units: Participants	0	0		

Notes:

[129] - mITT Population

[130] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hemoglobin, total protein, albumin and mean corpuscle hemoglobin concentration (MCHC) at the indicated time points

End point title	Change from Baseline in hemoglobin, total protein, albumin and mean corpuscle hemoglobin concentration (MCHC) at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate hemoglobin, total protein, albumin and MCHC. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[131]	90[132]		
Units: Gram (G)/Liter (L)				
arithmetic mean (standard deviation)				
Hemoglobin, Week 2 (n=85,82)	-0.3 (± 7.12)	0.0 (± 4.86)		
Hemoglobin, Week 4 (n=87,80)	-0.6 (± 7.01)	-1.0 (± 6.34)		
Hemoglobin, Week 8 (n=80,77)	-0.9 (± 8.38)	-2.5 (± 6.93)		
Hemoglobin, Week 12 (n=76,70)	-0.5 (± 7.61)	-1.4 (± 9.90)		
Hemoglobin, Week 18 (n=66,61)	0.1 (± 9.24)	-2.3 (± 9.66)		
Hemoglobin, Week 26 (n=52,50)	-0.7 (± 9.27)	-2.9 (± 8.86)		
Hemoglobin, Week 39 (n=28,29)	0.0 (± 11.71)	-0.1 (± 10.09)		
Hemoglobin, Week 52 (n=14,11)	2.9 (± 8.43)	-1.8 (± 7.90)		
Hemoglobin, Follow up (n=80,67)	-0.2 (± 9.30)	-4.5 (± 9.42)		
Albumin, Week 2 (n=90,84)	-0.3 (± 2.23)	-0.6 (± 2.55)		
Albumin, Week 4 (n=88,81)	-0.5 (± 2.35)	-0.3 (± 2.28)		
Albumin, Week 8 (n=81,79)	-1.1 (± 2.43)	-1.2 (± 2.38)		
Albumin, Week 12 (n=78,72)	-0.4 (± 2.62)	-0.8 (± 2.64)		
Albumin, Week 18 (n=67,60)	-1.1 (± 2.53)	-1.1 (± 2.32)		
Albumin, Week 26 (n=53,50)	-0.9 (± 2.89)	-1.1 (± 2.25)		
Albumin, Week 39 (n=28,29)	-0.8 (± 2.76)	-1.2 (± 2.35)		
Albumin, Week 52 (n=14,11)	-0.4 (± 2.95)	-1.5 (± 2.07)		
Albumin, Follow up (n=80,68)	-0.8 (± 2.49)	-1.6 (± 2.71)		
Total protein, Week 2 (n=90,84)	-0.4 (± 3.68)	-1.6 (± 2.96)		
Total protein, Week 4 (n=88,81)	-0.8 (± 3.93)	-1.2 (± 3.18)		
Total protein, Week 8 (n=81,79)	-1.8 (± 3.67)	-2.0 (± 3.01)		
Total protein, Week 12 (n=78,72)	-0.6 (± 4.14)	-0.8 (± 3.45)		
Total protein, Week 18 (n=67,60)	-0.8 (± 4.00)	-1.5 (± 2.66)		
Total protein, Week 26 (n=53,50)	-0.5 (± 4.59)	-1.5 (± 3.70)		
Total protein, Week 39 (n=28,29)	-0.6 (± 4.50)	-2.2 (± 3.51)		
Total protein, Week 52 (n=14,11)	-0.8 (± 4.66)	-3.0 (± 3.66)		
Total protein, Follow up (n=80,68)	-1.6 (± 4.05)	-2.0 (± 3.87)		
MCHC, Week 2 (n=85,82)	0.1 (± 6.94)	1.7 (± 6.40)		
MCHC, Week 4 (n=87,80)	0.3 (± 6.31)	-0.6 (± 6.80)		
MCHC, Week 8 (n=80,77)	-1.0 (± 7.63)	-0.9 (± 6.88)		
MCHC, Week 12 (n=76,70)	-3.1 (± 8.45)	-3.3 (± 10.70)		
MCHC, Week 18 (n=66,61)	-5.0 (± 10.38)	-4.8 (± 8.75)		
MCHC, Week 26 (n=52,50)	-4.4 (± 7.06)	-5.3 (± 8.48)		

MCHC, Week 39 (n=28,29)	-2.8 (± 5.19)	-1.5 (± 5.35)		
MCHC, Week 52 (n=14,11)	-3.9 (± 5.55)	-3.3 (± 6.15)		
MCHC, Follow up (n=80,67)	1.5 (± 9.77)	0.6 (± 8.73)		

Notes:

[131] - mITT Population

[132] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit at the indicated time points

End point title	Change from Baseline in hematocrit at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate hematocrit. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[133]	90[134]		
Units: Liter				
arithmetic mean (standard deviation)				
Hematocrit, Week 2 (n=85,82)	-0.001 (± 0.0238)	-0.002 (± 0.0169)		
Hematocrit, Week 4 (n=87,80)	-0.002 (± 0.0236)	-0.002 (± 0.0218)		
Hematocrit, Week 8 (n=80,77)	-0.001 (± 0.0274)	-0.006 (± 0.0229)		
Hematocrit, Week 12 (n=76,70)	0.002 (± 0.0251)	0.000 (± 0.0361)		
Hematocrit, Week 18 (n=66,61)	0.007 (± 0.0296)	0.000 (± 0.0337)		
Hematocrit, Week 26 (n=52,50)	0.003 (± 0.0302)	0.000 (± 0.0318)		
Hematocrit, Week 39 (n=28,29)	0.003 (± 0.0373)	0.001 (± 0.0329)		
Hematocrit, Week 52 (n=14,11)	0.014 (± 0.0231)	-0.001 (± 0.0255)		
Hematocrit, Follow up (n=80,67)	-0.003 (± 0.0305)	-0.015 (± 0.0302)		

Notes:

[133] - mITT Population

[134] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in absolute white blood cell (WBC) count, total neutrophil, total lymphocyte, basophil, eosinophil, monocyte and platelet count at the indicated time point

End point title	Change from Baseline in absolute white blood cell (WBC) count, total neutrophil, total lymphocyte, basophil, eosinophil, monocyte and platelet count at the indicated time point

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate absolute WBC count, total neutrophil, total lymphocyte, basophil, absolute eosinophil, percentage eosinophil, monocyte and platelet count. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[135]	90[136]		
Units: Giga cells per liter (GI/L)				
arithmetic mean (standard deviation)				
Absolute WBC count, Week 2 (n=85,82)	-0.04 (± 1.586)	0.21 (± 1.710)		
Absolute WBC count, Week 4 (n=86,80)	0.03 (± 1.742)	0.12 (± 2.116)		
Absolute WBC count, Week 8 (n=80,77)	0.04 (± 1.474)	0.32 (± 1.939)		
Absolute WBC count, Week 12 (n=76,70)	-0.07 (± 1.628)	0.51 (± 1.905)		
Absolute WBC count, Week 18 (n=66,60)	0.29 (± 1.921)	0.17 (± 1.842)		
Absolute WBC count, Week 26 (n=52,50)	-0.07 (± 1.625)	0.09 (± 1.876)		
Absolute WBC count, Week 39 (n=28,29)	0.29 (± 1.777)	1.08 (± 2.857)		
Absolute WBC count, Week 52 (n=14,11)	0.86 (± 1.687)	0.75 (± 1.637)		
Absolute WBC count, Follow up (n=79,67)	0.73 (± 1.691)	0.50 (± 2.195)		
Total neutrophils, Week 2 (n=85,82)	-0.038 (± 1.5980)	-0.080 (± 1.7982)		
Total neutrophils, Week 4 (n=86,80)	-0.014 (± 1.7572)	-0.012 (± 2.0753)		
Total neutrophils, Week 8 (n=80,77)	-0.052 (± 1.6060)	0.060 (± 2.0525)		
Total neutrophils, Week 12 (n=76,70)	0.023 (± 1.7039)	0.316 (± 2.0173)		
Total neutrophils, Week 18 (n=66,60)	0.189 (± 1.9556)	-0.161 (± 1.7378)		

Total neutrophils, Week 26 (n=52,50)	-0.067 (± 1.4529)	-0.190 (± 1.8779)		
Total neutrophils, Week 39 (n=28,29)	0.240 (± 1.7846)	0.689 (± 2.9389)		
Total neutrophils, Week 52 (n=14,11)	1.001 (± 1.8753)	0.248 (± 1.4497)		
Total neutrophils, Follow up (n=79,67)	0.555 (± 1.7317)	0.309 (± 2.3168)		
Total lymphocyte, Week 2 (n=85,82)	0.022 (± 0.4739)	0.282 (± 0.7058)		
Total lymphocyte, Week 4 (n=86,80)	0.043 (± 0.6599)	0.161 (± 0.5497)		
Total lymphocyte, Week 8 (n=80,77)	0.089 (± 0.5532)	0.263 (± 0.7366)		
Total lymphocyte, Week 12 (n=76,70)	-0.083 (± 0.5983)	0.210 (± 0.6986)		
Total lymphocyte, Week 18 (n=66,60)	0.076 (± 0.4751)	0.321 (± 0.6855)		
Total lymphocyte, Week 26 (n=52,50)	-0.042 (± 0.6673)	0.296 (± 0.7236)		
Total lymphocyte, Week 39 (n=28,29)	0.019 (± 0.4731)	0.387 (± 0.6355)		
Total lymphocyte, Week 52 (n=14,11)	-0.107 (± 0.4707)	0.449 (± 0.5762)		
Total lymphocyte, Follow up (n=79,67)	0.100 (± 0.5969)	0.090 (± 0.6346)		
Basophils, Week 2 (n=85,82)	0.000 (± 0.0194)	0.002 (± 0.0290)		
Basophils, Week 4 (n=86,80)	-0.001 (± 0.0332)	-0.002 (± 0.0231)		
Basophils, Week 8 (n=80,77)	-0.003 (± 0.0288)	0.003 (± 0.0254)		
Basophils, Week 12 (n=76,70)	0.001 (± 0.0328)	0.000 (± 0.0212)		
Basophils, Week 18 (n=66,60)	-0.002 (± 0.0249)	-0.002 (± 0.0191)		
Basophils, Week 26 (n=52,50)	0.001 (± 0.0241)	-0.006 (± 0.0173)		
Basophils, Week 39 (n=28,29)	-0.001 (± 0.0180)	-0.005 (± 0.0190)		
Basophils, Week 52 (n=14,11)	-0.006 (± 0.0109)	0.000 (± 0.0184)		
Basophils, Follow up (n=79,67)	-0.004 (± 0.0305)	0.000 (± 0.0234)		
Eosinophil, Week 2 (n=85,82)	0.000 (± 0.0660)	0.025 (± 0.0941)		
Eosinophil, Week 4 (n=86,80)	-0.002 (± 0.1092)	0.013 (± 0.0713)		
Eosinophil, Week 8 (n=80,77)	0.008 (± 0.0948)	0.014 (± 0.0918)		
Eosinophil, Week 12 (n=76,70)	-0.001 (± 0.0817)	0.013 (± 0.1173)		
Eosinophil, Week 18 (n=66,60)	0.030 (± 0.1287)	0.046 (± 0.1926)		
Eosinophil, Week 26 (n=52,50)	0.037 (± 0.1554)	0.051 (± 0.1646)		
Eosinophil, Week 39 (n=28,29)	0.037 (± 0.0628)	0.028 (± 0.1035)		
Eosinophil, Week 52 (n=14,11)	-0.001 (± 0.0539)	0.006 (± 0.1688)		
Eosinophil, Follow up (n=79,67)	0.011 (± 0.0935)	0.025 (± 0.0903)		

Monocytes, Week 2 (n=85,82)	-0.029 (± 0.1598)	-0.024 (± 0.1898)		
Monocytes, Week 4 (n=86,80)	0.002 (± 0.1404)	-0.029 (± 0.1975)		
Monocytes, Week 8 (n=80,77)	0.001 (± 0.1785)	-0.014 (± 0.1653)		
Monocytes, Week 12 (n=76,70)	-0.007 (± 0.1709)	-0.026 (± 0.2145)		
Monocytes, Week 18 (n=66,60)	-0.010 (± 0.2023)	-0.025 (± 0.2235)		
Monocytes, Week 26 (n=52,50)	0.001 (± 0.2093)	-0.057 (± 0.1790)		
Monocytes, Week 39 (n=28,29)	-0.005 (± 0.1210)	-0.020 (± 0.2376)		
Monocytes, Week 52 (n=14,11)	-0.034 (± 0.1075)	0.020 (± 0.1511)		
Monocytes, Follow up (n=79,67)	0.071 (± 0.2319)	0.083 (± 0.2190)		
Platelet count, Week 2 (n=85,82)	-3.3 (± 45.84)	-2.3 (± 47.94)		
Platelet count, Week 4 (n=87,80)	-6.4 (± 41.43)	-0.4 (± 35.50)		
Platelet count, Week 8 (n=79,77)	-2.2 (± 40.51)	6.3 (± 53.31)		
Platelet count, Week 12 (n=75,70)	-10.0 (± 44.01)	5.1 (± 55.82)		
Platelet count, Week 18 (n=66,59)	5.3 (± 53.14)	3.2 (± 50.43)		
Platelet count, Week 26 (n=52,50)	-2.7 (± 48.66)	-0.4 (± 42.21)		
Platelet count, Week 39 (n=28,29)	-3.4 (± 35.47)	0.0 (± 45.29)		
Platelet count, Week 52 (n=14,11)	-13.6 (± 34.98)	-0.5 (± 30.06)		
Platelet count, Follow up (n=80,67)	9.7 (± 58.86)	10.5 (± 50.76)		

Notes:

[135] - mITT Population

[136] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in eosinophil percentage at the indicated time points

End point title	Change from Baseline in eosinophil percentage at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate eosinophil percentage. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[137]	90[138]		
Units: Percent change				
arithmetic mean (standard deviation)				
Eosinophil percentage, Week 2 (n=85,82)	0.09 (± 0.969)	0.30 (± 0.995)		
Eosinophil percentage, Week 4 (n=86,80)	0.03 (± 1.583)	0.16 (± 0.930)		
Eosinophil percentage, Week 8 (n=80,77)	0.14 (± 1.419)	0.11 (± 1.248)		
Eosinophil percentage, Week 12 (n=76,70)	0.08 (± 1.087)	0.08 (± 1.517)		
Eosinophil percentage, Week 18 (n=66,60)	0.30 (± 1.513)	0.60 (± 2.387)		
Eosinophil percentage, Week 26 (n=52,50)	0.58 (± 2.390)	0.58 (± 2.082)		
Eosinophil percentage, Week 39 (n=28,29)	0.39 (± 0.865)	0.21 (± 1.434)		
Eosinophil percentage, Week 52 (n=14,11)	-0.11 (± 0.805)	0.05 (± 2.819)		
Eosinophil percentage, Follow up (n=79,67)	-0.01 (± 1.245)	0.29 (± 1.215)		

Notes:

[137] - mITT Population

[138] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in total bilirubin, direct bilirubin, uric acid and creatinine at the indicated time point

End point title	Change from Baseline in total bilirubin, direct bilirubin, uric acid and creatinine at the indicated time point

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate total bilirubin, direct bilirubin, urice acid and creatinine. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[139]	90[140]		
Units: Micromole (UMOL)/ L				
arithmetic mean (standard deviation)				
Total bilirubin, Week 2 (n=90,84)	-0.5 (± 3.12)	0.2 (± 3.62)		

Total bilirubin, Week 4 (n=88,81)	0.2 (± 3.07)	-0.1 (± 2.97)		
Total bilirubin, Week 8 (n=81,79)	-0.4 (± 3.03)	-0.7 (± 3.28)		
Total bilirubin, Week 12 (n=78,72)	-0.2 (± 3.33)	-0.1 (± 3.56)		
Total bilirubin, Week 18 (n=67,60)	0.0 (± 3.84)	0.2 (± 2.66)		
Total bilirubin, Week 26 (n=53,50)	0.0 (± 3.03)	-0.5 (± 3.05)		
Total bilirubin, Week 39 (n=28,29)	0.0 (± 2.06)	0.2 (± 3.55)		
Total bilirubin, Week 52 (n=14,11)	1.1 (± 3.38)	0.9 (± 2.91)		
Total bilirubin, Follow up (n=80,68)	0.2 (± 3.62)	-0.4 (± 2.67)		
Direct bilirubin, Week 2 (n=90,84)	-0.1 (± 1.09)	0.2 (± 1.04)		
Direct bilirubin, Week 4 (n=88,81)	0.1 (± 0.89)	0.0 (± 0.94)		
Direct bilirubin, Week 8 (n=81,79)	0.0 (± 0.92)	-0.1 (± 0.98)		
Direct bilirubin, Week 12 (n=78,72)	0.1 (± 0.92)	0.3 (± 1.17)		
Direct bilirubin, Week 18 (n=67,60)	0.1 (± 1.00)	0.2 (± 0.98)		
Direct bilirubin, Week 26 (n=53,50)	-0.1 (± 0.79)	0.0 (± 1.14)		
Direct bilirubin, Week 39 (n=28,29)	-0.1 (± 0.72)	0.1 (± 0.88)		
Direct bilirubin, Week 52 (n=14,11)	-0.1 (± 1.14)	0.1 (± 0.70)		
Direct bilirubin, Follow up (n=80,68)	0.1 (± 1.09)	0.0 (± 0.96)		
Uric acid, Week 2 (n=90,83)	1.7 (± 44.47)	-7.0 (± 45.87)		
Uric acid, Week 4 (n=88,80)	-3.8 (± 53.43)	-14.0 (± 44.47)		
Uric acid, Week 8 (n=81,78)	2.1 (± 47.41)	-12.1 (± 52.91)		
Uric acid, Week 12 (n=78,71)	7.5 (± 54.68)	-10.2 (± 62.09)		
Uric acid, Week 18 (n=67,60)	6.7 (± 49.87)	-5.9 (± 54.33)		
Uric acid, Week 26 (n=53,50)	0.6 (± 54.09)	-3.7 (± 61.19)		
Uric acid, Week 39 (n=28,29)	13.7 (± 50.99)	16.6 (± 87.59)		
Uric acid, Week 52 (n=14,11)	7.9 (± 48.23)	8.3 (± 57.49)		
Uric acid, Follow up (n=80,67)	-2.6 (± 62.22)	1.7 (± 63.56)		
Creatinine, Week 2 (n=90,84)	0.20 (± 7.974)	3.22 (± 9.140)		
Creatinine, Week 4 (n=88,81)	0.04 (± 7.224)	1.78 (± 9.899)		
Creatinine, Week 8 (n=81,79)	0.53 (± 11.111)	2.23 (± 10.424)		
Creatinine, Week 12 (n=78,72)	-0.11 (± 9.917)	3.46 (± 17.547)		
Creatinine, Week 18 (n=67,60)	0.41 (± 11.973)	5.32 (± 18.863)		
Creatinine, Week 26 (n=53,50)	1.61 (± 8.018)	1.30 (± 8.927)		
Creatinine, Week 39 (n=28,29)	2.16 (± 6.164)	5.64 (± 12.546)		
Creatinine, Week 52 (n=14,11)	2.94 (± 6.757)	0.33 (± 5.150)		
Creatinine, Follow up (n=80,68)	0.62 (± 12.075)	0.23 (± 9.463)		

Notes:

[139] - mITT Population

[140] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyl transferase at the indicated time points

End point title	Change from Baseline in alanine aminotransferase, aspartate

	aminotransferase, alkaline phosphatase and gamma glutamyl transferase at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyl transferase at the indicated time point. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[141]	90[142]		
Units: International units (IU)/ L				
arithmetic mean (standard deviation)				
Alanine aminotransferase, Week 2 (n=90,84)	-0.3 (± 3.78)	1.2 (± 5.52)		
Alanine aminotransferase, Week 4 (n=88,81)	1.8 (± 8.22)	0.3 (± 6.56)		
Alanine aminotransferase, Week 8 (n=81,79)	-0.3 (± 6.00)	-0.1 (± 6.53)		
Alanine aminotransferase, Week 12 (n=78,72)	1.3 (± 9.61)	1.7 (± 7.48)		
Alanine aminotransferase, Week 18 (n=67,60)	0.3 (± 8.03)	2.4 (± 7.67)		
Alanine aminotransferase, Week 26 (n=53,50)	-0.2 (± 7.88)	3.0 (± 10.79)		
Alanine aminotransferase, Week 39 (n=28,29)	3.0 (± 14.98)	1.9 (± 9.74)		
Alanine aminotransferase, Week 52 (n=14,11)	-1.1 (± 5.79)	1.9 (± 3.24)		
Alanine aminotransferase, Follow up (n=80,68)	0.7 (± 12.02)	0.7 (± 6.86)		
Aspartate aminotransferase, Week 2 (n=90,84)	-0.5 (± 3.68)	1.4 (± 4.25)		
Aspartate aminotransferase, Week 4 (n=88,80)	2.0 (± 7.65)	0.5 (± 5.16)		
Aspartate aminotransferase, Week 8 (n=81,79)	-0.4 (± 6.54)	0.5 (± 5.13)		
Aspartate aminotransferase, Week 12 (n=78,72)	2.2 (± 11.91)	2.0 (± 7.73)		
Aspartate aminotransferase, Week 18 (n=67,60)	0.9 (± 5.72)	2.9 (± 6.25)		
Aspartate aminotransferase, Week 26 (n=53,49)	0.3 (± 5.75)	4.7 (± 9.94)		
Aspartate aminotransferase, Week 39 (n=28,29)	1.3 (± 6.50)	2.4 (± 9.79)		
Aspartate aminotransferase, Week 52 (n=14,11)	-1.1 (± 9.22)	1.7 (± 3.23)		
Aspartate aminotransferase, Follow up (n=80,67)	0.3 (± 6.55)	0.1 (± 4.56)		

Alkaline phosphatase, Week 2 (n=90,84)	0.3 (± 9.14)	-2.0 (± 11.62)		
Alkaline phosphatase, Week 4 (n=88,81)	0.0 (± 10.43)	-2.8 (± 10.32)		
Alkaline phosphatase, Week 8 (n=81,79)	-2.5 (± 10.46)	-5.3 (± 12.71)		
Alkaline phosphatase, Week 12 (n=78,72)	-2.9 (± 12.67)	-4.7 (± 12.64)		
Alkaline phosphatase, Week 18 (n=67,60)	1.0 (± 9.87)	-4.9 (± 13.57)		
Alkaline phosphatase, Week 26 (n=53,50)	0.2 (± 13.06)	-4.4 (± 16.89)		
Alkaline phosphatase, Week 39 (n=28,29)	0.9 (± 9.77)	-4.1 (± 22.29)		
Alkaline phosphatase, Week 52 (n=14,11)	0.1 (± 6.39)	-9.5 (± 9.37)		
Alkaline phosphatase, Follow up (n=80,68)	-4.2 (± 15.26)	-4.4 (± 13.57)		
Gamma glutamyl transferase, Week 2 (n=90,84)	-0.3 (± 11.45)	-1.5 (± 16.55)		
Gamma glutamyl transferase, Week 4 (n=88,81)	1.4 (± 19.82)	-3.7 (± 19.85)		
Gamma glutamyl transferase, Week 8 (n=81,79)	-1.8 (± 17.32)	-5.3 (± 20.20)		
Gamma glutamyl transferase, Week 12 (n=78,72)	-0.1 (± 17.11)	-1.1 (± 24.97)		
Gamma glutamyl transferase, Week 18 (n=67,60)	0.6 (± 15.42)	-1.7 (± 21.15)		
Gamma glutamyl transferase, Week 26 (n=53,50)	-1.8 (± 13.53)	2.5 (± 19.87)		
Gamma glutamyl transferase, Week 39 (n=28,29)	-1.7 (± 10.4)	1.4 (± 25.46)		
Gamma glutamyl transferase, Week 52 (n=14,11)	-0.5 (± 13.39)	0.1 (± 9.06)		
Gamma glutamyl transferase, Follow up (n=80,68)	-2.5 (± 17.16)	0.1 (± 14.92)		

Notes:

[141] - mITT Population

[142] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in chloride, calcium, glucose, potassium, sodium and blood urea nitrogen at the indicated time points

End point title	Change from Baseline in chloride, calcium, glucose, potassium, sodium and blood urea nitrogen at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate calcium, chloride, glucose, potassium, sodium and blood urea nitrogenat the indicated time point. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[143]	90[144]		
Units: Millimole (MMOL)/L				
arithmetic mean (standard deviation)				
Chloride, Week 2 (n=90,84)	0.3 (± 2.59)	0.5 (± 2.40)		
Chloride, Week 4 (n=88,81)	-0.2 (± 2.42)	1.1 (± 2.51)		
Chloride, Week 8 (n=81,79)	0.3 (± 2.88)	0.7 (± 2.85)		
Chloride, Week 12 (n=77,72)	0.0 (± 2.48)	0.2 (± 2.93)		
Chloride, Week 18 (n=67,60)	0.2 (± 2.73)	0.3 (± 2.66)		
Chloride, Week 26 (n=53,50)	-0.3 (± 3.35)	0.5 (± 2.57)		
Chloride, Week 39 (n=28,29)	-0.8 (± 2.45)	0.1 (± 2.15)		
Chloride, Week 52 (n=14,11)	-1.8 (± 2.12)	-1.4 (± 2.66)		
Chloride, Follow up (n=80,68)	-0.2 (± 2.87)	-0.5 (± 2.24)		
Calcium, Week 2 (n=90,84)	-0.002 (± 0.1031)	-0.042 (± 0.0774)		
Calcium, Week 4 (n=88,80)	-0.024 (± 0.1007)	-0.31 (± 0.0908)		
Calcium, Week 8 (n=81,79)	-0.017 (± 0.0934)	-0.039 (± 0.0843)		
Calcium, Week 12 (n=78,72)	-0.008 (± 0.1106)	-0.029 (± 0.0982)		
Calcium, Week 18 (n=67,60)	-0.017 (± 0.0891)	-0.033 (± 0.0928)		
Calcium, Week 26 (n=53,49)	-0.024 (± 0.0855)	-0.023 (± 0.1014)		
Calcium, Week 39 (n=28,29)	-0.017 (± 0.0922)	-0.032 (± 0.0927)		
Calcium, Week 52 (n=14,11)	0.002 (± 0.1004)	-0.061 (± 0.0791)		
Calcium, Follow up (n=80,67)	-0.018 (± 0.1042)	-0.010 (± 0.0959)		
Glucose, Week 2 (n=90,84)	-0.13 (± 1.456)	0.22 (± 1.619)		
Glucose, Week 4 (n=88,81)	-0.01 (± 1.500)	0.04 (± 1.204)		
Glucose, Week 8 (n=81,79)	0.01 (± 1.330)	0.28 (± 1.272)		
Glucose, Week 12 (n=78,72)	-0.08 (± 1.661)	0.24 (± 1.439)		
Glucose, Week 18 (n=67,60)	0.22 (± 1.607)	0.50 (± 1.974)		
Glucose, Week 26 (n=53,50)	-0.08 (± 1.518)	0.00 (± 1.117)		
Glucose, Week 39 (n=28,29)	-0.11 (± 1.553)	-0.16 (± 1.202)		
Glucose, Week 52 (n=14,11)	0.31 (± 1.075)	-0.09 (± 0.896)		
Glucose, Follow up (n=80,68)	0.20 (± 1.645)	0.34 (± 2.104)		
Potassium, Week 2 (n=90,84)	0.02 (± 0.349)	-0.01 (± 0.391)		
Potassium, Week 4 (n=88,80)	0.01 (± 0.498)	0.06 (± 0.393)		
Potassium, Week 8 (n=81,79)	0.05 (± 0.406)	-0.03 (± 0.306)		

Potassium, Week 12 (n=77,72)	0.02 (± 0.352)	-0.06 (± 0.354)		
Potassium, Week 18 (n=67,60)	0.02 (± 0.390)	0.14 (± 0.525)		
Potassium, Week 26 (n=53,49)	0.02 (± 0.309)	-0.02 (± 0.381)		
Potassium, Week 39 (n=28,29)	0.13 (± 0.395)	-0.03 (± 0.415)		
Potassium, Week 52 (n=14,11)	0.10 (± 0.390)	-0.13 (± 0.422)		
Potassium, Follow up (n=80,67)	0.01 (± 0.385)	-0.02 (± 0.395)		
Sodium, Week 2 (n=90,84)	0.1 (± 2.16)	-0.2 (± 2.06)		
Sodium, Week 4 (n=88,81)	-0.1 (± 2.18)	0.3 (± 2.37)		
Sodium, Week 8 (n=81,79)	0.0 (± 2.33)	-0.1 (± 2.50)		
Sodium, Week 12 (n=77,72)	-0.1 (± 1.96)	-0.4 (± 2.39)		
Sodium, Week 18 (n=67,60)	0.1 (± 2.80)	-0.7 (± 2.49)		
Sodium, Week 26 (n=53,50)	0.1 (± 2.92)	-0.2 (± 1.83)		
Sodium, Week 39 (n=28,29)	-0.4 (± 2.33)	-0.3 (± 2.18)		
Sodium, Week 52 (n=14,11)	-0.6 (± 1.28)	-0.9 (± 1.45)		
Sodium, Follow up (n=80,68)	-0.2 (± 2.40)	-0.1 (± 2.14)		
Blood urea nitrogen, Week 2 (n=90,84)	-0.04 (± 1.368)	0.46 (± 1.474)		
Blood urea nitrogen, Week 4 (n=88,81)	-0.21 (± 1.399)	0.14 (± 1.392)		
Blood urea nitrogen, Week 8 (n=81,79)	-0.11 (± 1.635)	0.15 (± 1.464)		
Blood urea nitrogen, Week 12 (n=78,72)	-0.12 (± 1.511)	0.62 (± 1.993)		
Blood urea nitrogen, Week 18 (n=67,60)	-0.41 (± 1.332)	0.72 (± 2.310)		
Blood urea nitrogen, Week 26 (n=53,50)	-0.34 (± 1.267)	0.24 (± 1.636)		
Blood urea nitrogen, Week 39 (n=28,29)	-0.26 (± 1.385)	0.62 (± 1.680)		
Blood urea nitrogen, Week 52 (n=14,11)	0.01 (± 0.975)	1.07 (± 1.209)		
Blood urea nitrogen, Follow up (n=80,68)	0.07 (± 1.577)	0.11 (± 1.545)		

Notes:

[143] - mITT Population

[144] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Red blood cell count at the indicated time points

End point title	Change from Baseline in Red blood cell count at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate Red blood cell count. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[145]	90[146]		
Units: Trillion cells per liter (TI/L)				
arithmetic mean (standard deviation)				
Red blood cell count, Week 2 (n=85,82)	-0.01 (± 0.248)	0.00 (± 0.183)		
Red blood cell count, Week 4 (n=87,80)	-0.03 (± 0.242)	-0.02 (± 0.219)		
Red blood cell count, Week 8 (n=80,77)	-0.03 (± 0.281)	-0.05 (± 0.205)		
Red blood cell count, Week 12 (n=76,70)	0.02 (± 0.278)	0.02 (± 0.328)		
Red blood cell count, Week 18 (n=66,61)	0.04 (± 0.341)	0.00 (± 0.287)		
Red blood cell count, Week 26 (n=52,50)	0.01 (± 0.318)	-0.02 (± 0.268)		
Red blood cell count, Week 39 (n=28,29)	0.08 (± 0.352)	0.09 (± 0.265)		
Red blood cell count, Week 52 (n=14,11)	0.23 (± 0.320)	0.01 (± 0.230)		
Red blood cell count, Follow up (n=80,67)	0.06 (± 0.354)	-0.04 (± 0.280)		

Notes:

[145] - mITT Population

[146] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in mean corpuscle hemoglobin at the indicated time points

End point title	Change from Baseline in mean corpuscle hemoglobin at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate mean corpuscle hemoglobin. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[147]	90[148]		
Units: Picograms				
arithmetic mean (standard deviation)				
Mean corpuscle hemoglobin, Week 2 (n=85,82)	0.02 (± 0.551)	0.03 (± 0.701)		
Mean corpuscle hemoglobin, Week 4 (n=87,80)	0.09 (± 0.516)	-0.04 (± 0.480)		
Mean corpuscle hemoglobin, Week 8 (n=80,77)	0.02 (± 0.801)	-0.20 (± 0.700)		
Mean corpuscle hemoglobin, Week 12 (n=76,70)	-0.22 (± 0.773)	-0.46 (± 0.964)		
Mean corpuscle hemoglobin, Week 18 (n=66,61)	-0.27 (± 1.167)	-0.52 (± 0.944)		
Mean corpuscle hemoglobin, Week 26 (n=52,50)	-0.25 (± 0.692)	-0.48 (± 0.983)		
Mean corpuscle hemoglobin, Week 39 (n=28,29)	-0.55 (± 1.121)	-0.60 (± 1.100)		
Mean corpuscle hemoglobin, Week 52 (n=14,11)	-0.72 (± 1.022)	-0.32 (± 0.676)		
Mean corpuscle hemoglobin, Follow up (n=80,67)	-0.46 (± 1.130)	-0.73 (± 1.279)		

Notes:

[147] - mITT Population

[148] - mITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in mean corpuscle volume at the indicated time points

End point title	Change from Baseline in mean corpuscle volume at the indicated time points

End point description:

Blood samples were collected at Baseline (Day 1, pre-dose) and at Weeks 2, 4, 8, 12, 18, 26, 39, 52 (or at early withdrawal) and follow up (Week 53) to evaluate mean corpuscle volume. Values obtained at Day 1, pre-dose (Week 0) were considered as Baseline values. Change from Baseline was calculated as laboratory test value obtained at the indicated time point minus Baseline value. If post-dose value was missing for a particular assessment visit, then no derivation were performed and the change from Baseline were set to missing for that visit. Only those par. available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 53

End point values	Placebo	Losmapimod 15 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94[149]	90[150]		
Units: Femtoliters				
arithmetic mean (standard deviation)				

Mean corpuscle volume, Week 2 (n=85,82)	0.0 (± 1.72)	-0.4 (± 1.97)		
Mean corpuscle volume, Week 4 (n=87,80)	0.1 (± 1.66)	0.1 (± 1.88)		
Mean corpuscle volume, Week 8 (n=80,77)	0.2 (± 2.49)	-0.4 (± 2.11)		
Mean corpuscle volume, Week 12 (n=76,70)	0.3 (± 2.29)	-0.4 (± 2.45)		
Mean corpuscle volume, Week 18 (n=66,61)	0.6 (± 2.85)	-0.1 (± 3.12)		
Mean corpuscle volume, Week 26 (n=52,50)	0.5 (± 2.34)	0.2 (± 3.07)		
Mean corpuscle volume, Week 39 (n=28,29)	-1.0 (± 3.50)	-1.4 (± 3.82)		
Mean corpuscle volume, Week 52 (n=14,11)	-1.4 (± 3.15)	0.0 (± 2.05)		
Mean corpuscle volume, Follow up (n=80,67)	-1.9 (± 2.73)	-2.4 (± 3.36)		

Notes:

[149] - mITT Population

[150] - mITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment SAEs and non-serious AEs were collected from start of Investigational Medicinal Product (Week 0) until Week 53 including 1 Week of follow up.

Adverse event reporting additional description:

On-treatment SAEs and non-serious AEs are reported for mITT Population, comprised of all par. who were randomized to treatment and who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants with COPD received placebo orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of inhaled corticosteroid (ICS). Salbutamol metered dose inhaler (MDI) was provided as a rescue medication.

Reporting group title	Losmapimod 15mg

Reporting group description:

Participants with COPD received losmapimod 15 mg tablets orally, twice daily, approximately 12 hours apart and within 30 minutes after meals with a full glass of water for the duration of the treatment period in addition to standard of care, stratified according to whether a center collects sputum or not and current use of ICS. Salbutamol MDI was provided as a rescue medication.

Serious adverse events	Placebo	Losmapimod 15mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 94 (8.51%)	19 / 90 (21.11%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bile duct cancer			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer			

subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 94 (0.00%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileal ulcer			
subjects affected / exposed	1 / 94 (1.06%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 94 (2.13%)	7 / 90 (7.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 94 (1.06%)	4 / 90 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 94 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Losmapimod 15mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 94 (9.57%)	13 / 90 (14.44%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 94 (9.57%)	13 / 90 (14.44%)	
occurrences (all)	13	20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported